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Can Oxygen Transport Analysis Tell Us Why People with HFpEF Feel so Poorly?

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Heart failure (HF) with preserved ejection fraction (HFpEF) is a huge public health problem.[1] There is no proven effective treatment. Patients with HFpEF are not able to engage in physical activity without developing symptoms of dyspnea and fatigue. This diminishes quality of life and is associated with increased mortality.[1, 2]

To perform physical activity, we increase O_2 consumption (VO_2). Oxygen transport is accomplished through convective and diffusive processes. Convective transport involves two steps: introduction of O_2 into the lungs (alveolar ventilation, V_A) and then transport from the lungs to the periphery in the circulation (cardiac output, CO). Diffusive O_2 transport describes two additional steps: movement of O_2 across the alveolar-pulmonary capillary interface in the lung (D_L), and unloading of O_2 from hemoglobin in skeletal muscle capillaries (D_M), where mitochondria consume it to make ATP. Impairments in any or several of these steps can constrain the ability of the body to increase VO_2 and thus perform activity.

When patients with HF display low peak VO_2 it is often assumed that this reflects a deficit in CO. However, according to the Fick principle, VO_2 is equal to the product of CO and the arterial-venous O_2 content difference (AVO_2diff). Over twenty years ago Wilson and colleagues made the remarkable observation that one-quarter of patients with severe HF and reduced ejection fraction (HFrEF) actually display normal leg blood flow during exercise.[3] Despite adequate convective O_2 delivery, these patients developed profound leg fatigue and an accelerated increase in venous lactate, indicating a switch to anaerobic glycolysis. The patients were less able to increase AVO_2diff during exercise, and this drove their low peak VO_2 rather than poor CO.[3] More recently, Esposito et al. have shown that this peripheral limitation is driven primarily by low D_M,[4] and the importance of the periphery in HFrEF is now well-established.[3, 4]

The story in HFpEF is much the same. For years, it was believed that exercise limitation was exclusively caused by inadequate ventricular filling from diastolic dysfunction.[5] But then it was found that despite normal resting CO, patients with HFpEF display significant limitations in the ability to augment CO in response to exercise.[6–8] Others then reported that many patients with HFpEF also display limitations in the ability to increase AVO_2diff, much

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like what is seen in HFrEF.[9–13] However, AVO_2diff is determined by both convective and diffusive O_2 transfer, so the more specific role of D_M in HFpEF has remained unclear.

In this issue of Circulation, Houstis and colleagues present an interesting new theoretical analysis emphasizing the importance of both central and peripheral contributors in HFpEF.[14] The authors retrospectively examined data from 79 patients with HFpEF and 55 controls. Using expired gas analysis and arterial and mixed venous blood sampling, they examined individual steps of the O_2 pathway during peak exercise. Some components were directly measured, including V_A and CO. Others, such as D_L, D_M and mitochondrial respiration were not directly measured but were estimated using a number of simplifying assumptions.[14]

The authors found that peak VO_2 was reduced by 34% in patients with HFpEF as compared to controls.[14] This was coupled with reduced O_2 entry through the lungs, manifest as 36% and 31% reductions in V_A and D_L, respectively. Convective O_2 delivery from lungs to tissues was reduced by 31%, due mainly to a 27% reduction in CO but also a 5% reduction in hemoglobin. Peak exercise AVO_2diff was reduced in HFpEF, but only by 8%. This might suggest at first glance that the periphery is less important.

However, when CO drops, there is greater time available for O_2 diffusion in the capillaries.[7] This led the authors to propose that AVO_2diff should have been even higher in the HFpEF group.[14] To adjust for this, they plotted CO vs AVO_2diff during peak exercise in their control group, and then compared the observed AVO_2diff relative to CO in the HFpEF group with what would be expected based upon their control group curve. This adjustment inflated the AVO_2diff deficit dramatically, such that it became 26% lower in the HFpEF group.

While this adjustment makes sense for the reasons noted, an alternative argument could be made. Muscle perfusion is tightly coupled to O_2 requirements in man.[15] While the signals that regulate increased CO as muscle O_2 demand increases are as yet unresolved, it is clear that as venous O_2 content drops (and AVO_2diff increases), the body responds by providing more blood flow.[7, 15] The authors conclude that AVO_2diff should have been higher in HFpEF, but what if the heart was unable to respond to reduction in venous O_2 with sufficient increase in CO? If this were true, then the “true CO deficit” would have been even higher. The circularity of the Fick principle is problematic here, and this dilemma cannot be resolved given the cross sectional nature of this study.[14]

The authors found that the deficit in AVO_2diff was related to a 36% reduction in D_M in HFpEF.[14] This is a novel and important observation. D_M was calculated assuming that muscle venous O_2 tension was equal to that in the pulmonary artery. However, this is not the case, because the pulmonary artery sample contains mixed venous blood from the rest of the body that contains much higher O_2 content when compared to the effluent blood from the femoral veins. In order to optimally distribute blood flow during exercise, there must be vasodilation to areas in need, like skeletal muscle, and sympathetically-mediated vasoconstriction to non-exercising areas, like viscera and adipose. Regional vasodilation in skeletal muscle is mediated in part by NO and prostaglandin-induced vasodilation.[16] Patients with HFpEF have impaired NO availability, particularly in the microvasculature, so this

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might contribute to the impairment in D_M.[6] HFpEF patients are also commonly obese, and it could be that obligate perfusion to excess fat mass might cause an effective "macrovascular shunt" that diminishes proper matching of flow to metabolism—this could also contribute to a lower AVO_2diff.[17, 18] Conversely, microvascular shunting may occur within skeletal muscle in HFpEF, especially when there is increased intramuscular fat and reduced capillary density, as recently reported.[11, 12] Further study is needed to better understand the mechanisms of and treatment for D_M impairment in HFpEF.

Houstis and colleagues propose that the O_2 pathway enables ascertainment of the causes of exercise intolerance in HFpEF,[14] but we cannot infer causation from correlation. The differing peak workloads achieved in controls and HFpEF are especially confounding. As exercise intensity increases, there is greater enhancement in convective O_2 transport, as well as O_2 diffusion, both in the lungs and in skeletal muscle.[19] If HFpEF patients would have been able to exercise to higher load, would they have been able to achieve a higher D_M? The same question can be raised with all components of the O_2 pathway. Controls were required (by design) to display peak VO_2 that was >90% predicted, while HFpEF were required to display values <80%.[14] Therefore, differences in peak VO_2, as well the associated deficits in O_2 pathway components, are to some extent tautological. It would be interesting to evaluate whether similar differences would exist between cases and controls at matched workloads.

The authors found that the majority of HFpEF patients (97%) displayed limitations in multiple components of the O_2 pathway.[14] To extend the data further, they conducted a theoretical analysis to explore what the expected "boost" in peak VO_2 might be if they could fix one or more components of the O_2 pathway while holding others constant. After accounting for the hypothesized reduction in AVO_2diff from increased perfusion, isolated improvements in CO were predicted to lead to relatively modest increase in peak VO_2. While this may be the case, it is important to acknowledge that these predictions are speculative, based upon highly theoretical modeling equations, without in vivo human data. It is unknown to what extent increases in CO would truly compromise O_2 diffusion in the periphery in HFpEF when O_2 demand is high, as during exercise. Indeed, single leg exercise allows for increased muscle blood flow that improves VO_2 relative to muscle mass, without dramatically compromising D_M in patients with HFrEF.[4] These questions require further testing using appropriately controlled interventional experiments to be answered.

The biggest boost in peak VO_2 in the authors' analysis was observed by improving D_M, again supporting an important role of the periphery, and there was synergy from improving multiple components together, which was highly dependent upon the nature and magnitude of deficits in the O_2 pathway.[14] While the analytical modeling performed is elegant and intellectually appealing, it seems unlikely that we can accurately estimate the effects of correcting a single impairment in the O_2 pathway while expecting others to remain constant —a limitation that the authors acknowledge. It does seem reasonable to conclude that the plurality of abnormalities observed in most patients supports therapies targeting multiple components of the O_2 pathway, such as exercise training or inorganic nitrites, as are currently being tested.[20]

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Houstis et al. ponder whether O_2 pathway analysis might form the basis for a new taxonomy of HFpEF, with the idea of 'personalizing' the deficits.[14] While this is a laudable goal, it may be problematic using this approach for several reasons. First, diseases caused by a variety of different pathologies may converge to cause similar limitations in the periphery. Each of these is likely just as complex and heterogenous as HFpEF. Examples include not only HFrEF, as discussed, but other chronic diseases ranging from aortic stenosis, pulmonary arterial hypertension, and COPD to cancer. If we just relied on O_2 pathway analysis alone, we might lump these patients together and ignore the specific cardiac, pulmonary and/or vascular lesions that initially caused the problem. In other words, this sort of complexity is ubiquitous in human disease; it is not unique to HFpEF.

The authors imply in the discussion that their analysis was undertaken to link HF symptoms to their cause.[14] But HF symptoms are not equivalent to peak aerobic capacity. Indeed, most patients with HFpEF never achieve levels of VO_2 attained with maximal exercise testing during everyday life. The authors' analysis also assumes that all features of exercise intolerance can be simplified into terms of O_2 transport. But this neglects the impact of other important components in HFpEF, like elevated filling pressures, which may alter lung mechanics, gas diffusion, respiratory muscle function, and right ventricular-pulmonary artery coupling, and are associated with symptoms, exercise capacity, and clinical outcomes.[8, 19–21] Indeed, it would be hard to imagine how peripheral impairments would cause pulmonary hypertension, right ventricular dysfunction, or the development of pulmonary edema in patients with acutely decompensated HF.

So can we assume that the factors that restrict O_2 consumption at the limits of peak endurance explain the symptoms that develop during everyday activities for patients? Probably not, but that doesn't mean that targeting these limitations won't be helpful. Why do patients with HFpEF feel so poorly when they exert themselves? The answer is the same in HFpEF as it is in HFrEF, and many other disorders: it's complicated. The novel and important insights provided by Houstis and colleagues in their elegant study have vertically advanced our understanding to make it a bit less complicated, while raising many more important new hypotheses that can be tested in the years to come.

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